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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/729,039	12/05/2003	James A. Williams	D-2939CIPCONDIV4	5294

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EXAMINER	
PORTNER, VIRGINIA ALLEN	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 06/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/729,039	WILLIAMS, JAMES A.	
	Examiner	Art Unit	
	Ginny Portner	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 February 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-31* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/17/05;5/17/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Amended claims 25-31 are pending.

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

1. The information disclosure statement filed February 17, 2005 and May 17, 2005 have been considered.

Objections/Rejections Withdrawn

1. The rejection of claims 25, 27 and 31 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2-5,9,12-14, 24,28 (in light of the definition provided for targeting ligand comprising an amino acid component at col. 6, lines 57-62 and col. 45-65 that is the C-terminal heavy chain) and claim 31 of U.S. Patent No. 6,787,517, is herein withdrawn in light of Applicant's amendments to the claims, and new grounds of rejection set forth below.

1. The objection to claims 25 and 28 for informalities has been obviated by Applicant's amendments to the claims.

2. The rejection of claims 25-31 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for recite the phrase "C-terminal portion" and "an N-terminal portion" has been obviated through amendment of the claims to recite functional limitations for the C-terminal portion and deletion of the claim limitations directed to the N-terminal portion.

3. The rejection of claims 25-26, 29-31 under 35 U.S.C. 102(b) as being anticipated by Whelan et al (1992), has been obviated through amendment of the claims to comprise a C-terminal portion.

4. The rejection of claims 25-26, 29-31 under 35 U.S.C. 102(b) as being anticipated by Campbell et al (1997, SWISS-PROT accession number Q60393) has been obviated through amendment of the claims to comprise a C-terminal portion.

5. The rejection of claims 25-26, 28 under 35 U.S.C. 102(b) as being anticipated by Maisey et al (1988), has been obviated through amendment of the claims to comprise a C-terminal portion.

Rejections Maintained

6. Amended claims 25-29, 31 remain rejected under 35 U.S.C. 102(e) as being anticipated by Dolly et al (US Pat. 6,203,794, effective filling date May 31, 1994) for reasons of record and responses set forth below.

7. Claims 25-26, 28 are rejected under 35 U.S.C. 102(a) as being anticipated by WO94/21684,) for reasons of record and responses set forth below.

Response to Arguments

8. The rejection of claims 25-29, 31 under 35 U.S.C. 102(e) as being anticipated by Dolly et al (US Pat. 6,203,794, effective filling date May 31, 1994) is traversed on the ground that Dolly et al does not suggest or teach a composition that comprises a soluble recombinant botulinum toxin protein.

9. With respect to Applicant's assertion that the botulinum toxin of Dolly et al would not be soluble, Ledoux et al (1994) is being cited to show and to provide evidence that botulinum neurotoxins are water soluble toxins (see abstract, page 1095, Ledoux et al).

10. Additionally, it is the position of the examiner that Dolly et al does disclose the use of "both native and recombinant wild-type Clostridial neurotoxin proteins (see col. 7, lines 32-35) as transporters which includes botulinum neurotoxin heavy chains (see col. 7, lines 32-35) that comprise the C-terminal fragment (heavy chain targeting portion, Dolly et al, claim 4, and col. 5, lines 12-14). While the reference does not exemplify this embodiment, the reference does constructive reduce this embodiment to practice for botulinum toxins B, C,D,E, F, and G (see Dolly et al, col. 7, lines 18-30, and col. 41, claims 2-3).

11. The recombinant expression of the Clostridial neurotoxin proteins are disclosed for expression in E.coli (see Dolly, col. 5, lines 38-52), which is a bacteria that grows under aerobic conditions.

12. While the instant claims recite the process limitation of "recombinant" no structural or functional characteristics that are not naturally present in the native neurotoxin protein are

claimed. While the term "recombinant" shows the hand of man, the resultant structure of the recombinant protein is identical to that of the native neurotoxin protein, as no distinguishing sequences, amino acid sequences or post-translational modifications have been set forth in the claims. Dolly et al still anticipates the instantly claimed invention as now claimed.

13. Applicant asserts that compositions of Dolly et al comprise a recombinant light chain and uses MBP in the formation of the botulinum toxin and the present claims are directed to composition that comprise the C-terminal portion of a heavy chain of botulinum toxin.

It is the position of the examiner that Dolly et al's compositions comprise the C-terminal portion of a heavy chain (see Dolly et al col. 7, lines 32-35, that comprise the C-terminal fragment,(heavy chain targeting portion, Dolly et al, claim 4, and col. 5, lines 12-14) of botulinum toxin (see Dolly et al, col. 7, lines 18-30, and col. 41, claims 2-3). Applicant's compositions do not exclude the presence of additional botulinum neurotoxin chains and therefore still read on the compositions disclosed in Dolly et al for reasons of record and responses set forth above.

14. The rejection of claims 25-26, 28 under 35 U.S.C. 102(a) as being anticipated by WO94/21684 is traversed on the grounds that WO94/21684 does not disclose, teach or even suggest a composition comprising a soluble recombinant botulinum toxin that comprises a C-terminal portion of botulinum toxin and that the portions of WO94' are less than 35 amino acids in length.

15. It is the position of the examiner that WO94' discloses a plurality of embodiments, and at page 5, paragraph 1-3, Experiment 2, Table 6, page 20 and claims 13-14, WO94/21684 disclose

the instantly amended and claimed invention directed to a composition that comprises botulinum toxin heavy chains of serotypes B, C, D and E, the heavy chains comprising H_C receptor binding domain for serotypes B, C and F (see Table 6, Expt. 2), wherein the neurotoxin protein was in solution (pharmaceutical excipient) carrier (see page 5, paragraphs 1-3 and claim 13-14). Ledoux et al (1994) is being cited to show and to provide evidence that botulinum neurotoxins are water soluble toxins (see abstract, page 1095, Ledoux et al) and therefore would be a soluble botulinum toxin.

16.

No distinguishing characteristics have been set forth in the claims to show that the claimed product by process "recombinant" limitation would not be the same or equivalent heavy chain obtained by a different process, specifically purified from natural sources. The reference still anticipates the instantly claimed invention.

New Claim Limitations/New Grounds of Rejection

Double Patenting

17. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

18. Claims 25-30 are directed to the same invention as that of claim 10 of commonly assigned 5,919,665. Claims 25-30 are rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 10 of prior U.S. Patent No. 5,919,665. This is a double patenting rejection. The conflicting claims not patentably distinct from each other because the allowed claim 10 is directed to genus of a fusion proteins of a Clostridium botulinum C fragment (abstract, first sentence) linked to a polyhistidine tract (tag) which is defined to include any serotype of A-G (' 665, col. 4, lines 28-43) and the instantly claimed invention is directed to specific serotype species, specifically types B, C1, D, E, F and G. The allowed genus claim encompasses the instantly claimed composition defined by a plurality of species of Clostridium botulinum toxin fragment C toxin proteins fused into a single polypeptide chain and is coupled to a poly-histidine tract (tag).

19. Claims 25-26 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1, 9,12-14 of U.S. Patent No. 6,787,517 (same assignee, Allergen/Ophidian, same as Application 08/704,159 to which the instant Application claims priority). Although the conflicting claims are not identical, they are not patentably distinct from each other because the allowed species claims anticipates the instantly claimed genus; specifically allowed claims 1, 2,9,12-14 of U.S. Patent No. 6,787,517 are directed to genus of a Clostridium botulinum toxin proteins that comprise the heavy chain ('517, claim 12; and col. 8, lines. 30-43) which comprises the receptor binding domain C fragment, wherein the heavy chain may be serotype of B, C1, D, E, F and G ('517, see definition at col. 6, lines 57-62, and claim 14), wherein the disclosed and the instantly claimed invention is directed to specific

serotype species, specifically types B, C1, D, E, F and G, which are disclosed as being able to be produced recombinantly based upon the coding sequence of each gene (see '517, claim 37, col. 37, line 2 and narrative through the patent).

Claim Rejections - 35 USC § 103

20. Claim 30 is rejected under 35 U.S.C. 103(a) as being unpatentable over Dolly et al as applied to claims 25-29, and 31 above in view of Williams et al (US Pat. 5,601,823).

1. See discussion of Dolly et al above. Dolly et al teach recombinant botulinum neurotoxin proteins that comprise the heavy chain C-terminal fragment that is capable of being expressed in an aerobic bacteria and is produced as a single polypeptide chain, wherein the single polypeptide chain comprises an additional maltose binding protein polypeptide sequence coupled to the botulinum toxin but differs from the instantly claimed invention by failing to show the additional coupled polypeptide to be a polyhistidine tract.

2. Williams et al teaches the production of recombinantly produced clostridium (botulinum and difficile(see col. 3, lines 25-29)) toxins as single chain polypeptides (see col. 8, lines 13-22, lines 59-63) either through coupling the toxin to a maltose binding protein polypeptide or to a polyhistidine tract polypeptide (see col. 35, lines 26-49, Example 11) in an analogous art for the purpose of producing large quantities of recombinant toxins for formulation of vaccines and generation of neutralizing antibodies induced to the recombinant clostridium toxins.

3. It would have been obvious to the person of ordinary skill at the time the invention was made to modify the recombinant polypeptide of Dolly et al that comprised a maltose binding protein non-toxin protein with the polyhistidine tract of Williams et al because Williams et al teaches and shows the successful production of recombinant clostridium toxins and teaches

prokaryotic expression systems for the attainment of recombinant Clostridial toxins through expression of single polypeptide chains, wherein the single polypeptide chains will bind to a ligand containing column to aid in protein isolation and purification, the polypeptides including either a maltose binding protein or a polyhistidine tract polypeptide tag (pET16b) (see Example 11, column 35), and these methods serve to define means for attainment of high levels of recombinant toxin.

4. The person of ordinary skill in the art would have been motivated by the reasonable expectation of success of obtaining a botulinum C-terminal portion recombinant protein that comprises a polyhistidine tract utilizing the expression system of Williams et al because both Dolly et al and Williams teach the utilization of maltose binding protein expression system for the recombinant expression of Clostridial toxins and Williams also successfully showed the recombinant expression of a Clostridial toxin using a polyhistidine tract polypeptide which provides the advantage of attaching the polypeptide polyhistidine tract either at the C-terminal end (pET23a-c) or the N-terminal end (pET16b) (see Example 11, col. 35, lines 26-49) of the Clostridial polypeptide depending on the preferred location of the non-toxin polyhistidine tract polypeptide. In the absence of a showing of unexpected results, Dolly et al in view of Williams et al obviate the instantly claimed invention.

Conclusion

2. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

3. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (571) 272-0862. The examiner can normally be reached on M-F, alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Vgp
May 26, 2005

Please Note: In light of the claimed invention requiring the recombinant botulinum toxin to comprise the recited portions the claimed toxins read on isolated complete botulinum toxins. Additionally the recitation of the term "recombinant" is being read as a process limitation, and the claimed toxin reads on the naturally occurring toxins absent claiming distinguishing characteristics that differ from that which occurs in nature, as no structural differences are encompassed by what is now claimed from that which would be present in an isolated botulinum toxin produced by natural sources.

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